

What is claimed is:

1. A polyprotein comprising external immunogens of membrane-associated proteins of variola major or immunologically cross-reactive poxviruses.
2. An immunogenic composition comprising the polyprotein of claim 1.
3. An isolated nucleic acid encoding the polyprotein of claim 1.
4. An immunogenic composition comprising the nucleic acid of claim 3.
5. A eukaryotic cell comprising the nucleic acid of claim 3.
6. The eukaryotic cell of claim 5, wherein the eukaryotic cell is a mammalian cell.
7. The polyprotein of claim 1 wherein the immunologically cross-reactive poxvirus is vaccinia virus.
8. A polyprotein comprising external immunogens of at least two poxvirus membrane-associated proteins selected from the group consisting of:
M1R, A36R, I5R, B7R, F8L, A30L, L1R, A33R, H5R, B5R, D8L and A27L .
9. The polyprotein of claim 8 comprising external immunogens of M1R, A30L, and A36R.
10. A polyprotein comprising external immunogens of at least two membrane-associated proteins, wherein antibodies against one of the proteins are synergistic with antibodies against the at least one other protein.
11. The polyprotein of claim 10 wherein the synergistic antibodies recognize A36R of variola major or A33R of vaccinia.
12. A method of inducing an antibody response comprising:
administering the polyprotein of claim 1 or 8 to a mammal.
13. A method of inducing an antibody response comprising:
administering the immunogenic composition of claim 2 or 4 to a mammal.
14. A method of making an immunogen comprising:
identifying a vaccinia protein that induces neutralizing or synergistic antibodies;
aligning the protein sequence of the vaccinia protein with its variola homolog;

- synthesizing a nucleic acid sequence encoding at least an external segment of the variola protein; and
- causing said nucleic acid to be expressed as a polypeptide.
15. The method of claim 14 wherein the causing step comprises transformation of a eukaryotic cell in vitro.
16. The method of claim 14 wherein the causing step comprises administration of the nucleic acid to a mammal.
17. A method of making an immunogen comprising:
- identifying a vaccinia protein that induces neutralizing or synergistic antibodies;
- aligning the protein sequences of multiple isolates of the vaccinia protein with multiple isolates its variola homolog;
- determining a variola consensus sequence;
- synthesizing a nucleic acid sequence encoding at least an external segment of said consensus sequence; and
- causing said nucleic acid to be expressed as a polypeptide.
18. An immunogenic composition comprising an immunogen made according to claim 14 or 17.
19. An immunogenic composition comprising a cocktail of immunogens made according to claim 14 or 17.
20. An immunogenic composition comprising a complex of polypeptides wherein each polypeptide comprises an external immunogen of a membrane-associated protein of variola major or immunologically cross-reactive poxviruses.
21. The immunogenic composition of claim 18 wherein the polypeptides are biotinylated and the complex is formed by the addition of avidin or streptavidin.
22. The immunogenic composition of claim 18 wherein the complex is formed by anchoring the polypeptides in a liposome or micelle.
23. A polyprotein comprising external immunogens of membrane-associated proteins of variola major or immunologically cross-reactive poxviruses wherein the individual proteins are joined through a linker-spacer peptide.

24. The polyprotein of claim 23 wherein the linker-spacer peptide has the sequence GGGGSSGG.
25. The polyprotein of claim 23 further comprising an affinity tag.
26. The polyprotein of claim 25 wherein the affinity tag is a poly-histidine tag.